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The role of attributable fraction in the exposed (AFE) in assessing the association of microorganisms with pneumonia

Xin Wang¹, You Li¹, Harish Nair¹

¹ Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics,
University of Edinburgh, Edinburgh, Scotland, UK

Keywords: attributable fraction in the exposed (AFE); association; pneumonia; children;
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Corresponding author: Xin Wang

Email: Xin.Wang-2@ed.ac.uk

Alternative corresponding author: You Li

Email: You.Li2@ed.ac.uk

Dear editor,

Recently, the interesting work by Benet et al [1] was published in *Clinical Infectious Diseases* assessing the association between microorganisms and radiographically confirmed primary end-point pneumonia requiring hospital admission in children aged 2–60 months [2]. In this prospective, multicentre, case-control study, the authors quantified the associations by calculating the adjusted population attributable fraction (aPAF) based on odds ratios (ORs) adjusting for gender, age, time period, site and the presence of other pathogens. Despite of the importance of aPAFs in evaluating the impact of these pathogens on pneumonia, the pooled aPAFs could not account for the wide variation in the pathogen positivity among cases between sites (e.g., 34–86% for *Streptococcus pneumoniae*; 7–44% for respiratory syncytial virus). This limits the generalization of the pooled aPAFs to developing countries. Therefore, we recommended that adjusted attributable fraction in the exposed (aAFE) be used to quantify the association between pathogens and pediatric pneumonia as in previous studies [3, 4]. Unlike PAF, AFE depends on the site-adjusted ORs alone, so it allows the input of pathogen positivity among cases at one site to calculate the site-specific PAF or that of site-specific burden of pneumonia positive for a given pathogen to benefit interpretation.

We calculated aAFE based on the adjusted ORs from the paper (Table 1). The aAFE estimates were calculated using Monte Carlo Simulation, with the median value of 10,000 samples simulated from the log-normal distributions of aOR per pathogen and age group as the point estimate, and the 2.5th and 97.5th percentiles as the 95% confidence interval. Of note, although rhinovirus had the third highest aPAF, it had a lower aAFE (44%) compared to many viruses including influenza virus, respiratory syncytial virus, parainfluenza virus 1, 3, 4, and human metapneumovirus in children <5 years, similar to the findings in a systematic review [5]. Rhinovirus is commonly isolated from upper respiratory specimens in healthy individuals as well as those with upper respiratory infection; this may largely explain its high aPAF. This study was conducted mostly in populations with very low PCV vaccine coverage. Further studies investigating the association of multiple pathogens in children with pneumonia in areas with higher coverage will help refine the AFE estimates.

Notes

Potential conflicts of interest. All authors: No reported conflicts of interest.

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Table 1. Adjusted attributable fraction in the exposed (aAFE, %) of microorganisms associated with pneumonia in children by age group (months) ^{1, 2, 3}.

Microorganisms	aAFE (% [95% confidence interval])			
	2–60 m	2–11 m	12–23 m	24–60 m
Mycoplasma pneumoniae	89 (62–97)	NA	NA	90 (41–98)
Streptococcus pneumoniae	62 (51–70)	66 (49–76)	62 (39–75)	62 (44–73)
Enterovirus	NA	NA	76 (30–91)	NA
Influenza A	98 (87–100)	NA	97 (78–100)	NA
Influenza B	70 (35–85)	NA	NA	NA
Human metapneumovirus	91 (82–95)	85 (54–95)	92 (74–97)	92 (65–98)
Parainfluenza virus 1	87 (66–94)	NA	NA	NA
Parainfluenza virus 3	85 (73–92)	78 (43–91)	90 (72–96)	90 (60–97)
Parainfluenza virus 4	62 (13–82)	NA	NA	NA
Rhinovirus	44 (28–57)	NA	56 (29–73)	41 (10–61)
Respiratory syncytial virus	92 (87–94)	95 (89–98)	91 (79–96)	78 (56–89)

¹ We only included the microorganisms whose lower bound of the 95% confidence intervals of adjusted odds ratios exceeded one.

² We assumed that the adjusted ORs (95% CIs) follow log-normal distributions. We simulated 10,000 samples based on each log-transformed aOR and 95% CIs for each-pathogen-age unit, using log-transformed point estimate as the mean, and using the log-transformed upper and lower limit to estimate the standard error. Then we back transformed the 10,000 samples and applied these samples in the function – adjusted attributable fraction in the exposed (aAFE) = (aOR–1)/aOR – to get the 10,000 samples of aAFE. From these samples, we used the median value as the point estimate of the aAFE, and 2.5 and 97.5 percentile as the 95% confidence intervals.

³ NA: not available.